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Carcinoma of the cervix and tobacco smoking: Collaborative reanalysis of individual data on 13,541 women with carcinoma of the cervix and 23,017 women without carcinoma of the cervix from 23 epidemiological studies

International Collaboration of Epidemiological Studies of Cervical Cancer*

Tobacco smoking has been classified as a cause of cervical cancer, but the effect of different patterns of smoking on risk is unclear. The International Collaboration of Epidemiological Studies of Cervical Cancer has brought together and combined individual data on 13,541 women with and 23,017 women without cervical carcinoma, from 23 epidemiological studies. Relative risks (RRs) and 95% confidence intervals (CIs) of carcinoma of the cervix in relation to tobacco smoking were calculated with stratification by study, age, sexual partners, age at first intercourse, oral contraceptive use and parity. Current smokers had a significantly increased risk of squamous cell carcinoma of the cervix compared to never smokers (RR = 1.60 (95% CI: 1.48–1.73), $p<0.001$). There was increased risk for past smokers also, though to a lesser extent (RR = 1.12 (1.01–1.25)), and there was no clear trend with time since stopping smoking (p-trend = 0.6). There was no association between smoking and adenocarcinoma of the cervix (RR = 0.89 (0.74–1.06) and 0.89 (0.72–1.10) for current and past smokers respectively), and the differences between the RRs for smoking and squamous cell and adenocarcinoma were statistically significant (current smoking $p<0.001$ and past smoking $p = 0.01$). In current smokers, the RR of squamous cell carcinoma increased with increasing number of cigarettes smoked per day and also with younger age at starting smoking ($p<0.001$ for each trend), but not with duration of smoking (p-trend = 0.3). Eight of the studies had tested women for cervical HPV-DNA, and in analyses restricted to women who tested positive, there was a significantly increased risk in current compared to never smokers for squamous cell carcinoma (RR = 1.95 (1.43–2.65)), but not for adenocarcinoma (RR = 1.06 (0.14–7.96)). In summary, smokers are at an increased risk of squamous cell but not of adenocarcinoma of the cervix. The risk of squamous cell carcinoma increases in current smokers with the number of cigarettes smoked per day and with younger age at starting smoking.

Key words: tobacco; cervical cancer; risk; meta-analysis

Cervical infection with high-risk types of human papillomavirus (HPV) is the main cause of most cervical cancers. Although many women get infected with this virus, most do not go on to develop cervical cancer. A number of other factors, such as tobacco smoking, are therefore thought to be involved in the disease process. The International Agency for Research on Cancer (IARC) has classified tobacco smoking as a cause of cervical cancer.[1] However, it remains unclear how different patterns of use, such as amount smoked or duration of smoking, affect a woman's risk of developing cervical cancer. Data on individual women from available epidemiological studies of cervical cancer and smoking behaviour were brought together and reanalysed to study this relationship in detail.

Material and methods

Identification of studies and collection of data

The International Collaboration of Epidemiological Studies of Cervical Cancer was set up primarily to study the effects of hormonal contraceptive use and other factors on the risk of cervical cancer. Epidemiological studies with an outcome of invasive cervical cancer or carcinoma *in situ*/cervical intraepithelial neoplasia grade 3 (CIN3) and information on hormonal contraceptive use were eligible for inclusion, and additionally, for the current paper, studies had to have collected information on tobacco smoking status (never/past/current smoker). Cohort (prospective) studies were eligible if they included at least 30 cases of invasive cervical cancer or carcinoma *in situ*/CIN3 and case–control studies were eligible if they had at least 100 invasive cancer cases or 200 carcinoma *in situ*/CIN3 cases. Studies were identified from review articles, from computer-aided literature searches and from discussions with colleagues. Efforts were made to identify all studies that included relevant information, whether or not results on smoking behaviour had been published. The principal investigators of all studies identified were invited to collaborate. A list of studies and references was given to collaborators and they were asked whether they knew of further studies; the principal investigators of those studies were also invited to collaborate. Few additional studies came to light as a result of these enquiries, and in view of the wide consultation it seems unlikely that any substantial studies have been missed. Analysis and presentation of the data were discussed by collaborators at the first meeting of collaborators at Lyon, in November 2003, and subsequently.

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Individual subject information was collected and analysed centrally to enable variables to be defined consistently across studies. Cohort studies were analysed as nested case–control studies with up to 4 controls (women without carcinoma of the cervix) selected randomly per case according to age (±1 year). Data on socioeconomic factors, smoking history, reproductive factors, sexual behaviour, hormonal and barrier contraceptive use and Pap smear history were collected and coded according to a standard format. A measurement of HPV infection was collected if available.

Histological classification of cancers was based on that described by the World Health Organisation (WHO) for tumours of the uterine cervix,[2] using, where possible, the original ICD codes reported for each woman. Invasive tumours, including those reported as microinvasive, were classed as specified squamous cell carcinoma, adenocarcinoma (including adenosquamous carcinoma), other types for which histology was available (including unspecified epithelial cancers, multiple types, *e.g.*, squamous cell with adenocarcinoma, and rare specified tumours) or 'histology unknown'. *In situ* cancers were classified as squamous cell (including unspecified CIN3) or specified adenocarcinoma *in situ*. Where invasive and *in situ* were both present, the cancer was classified as invasive. Benign and secondary tumours, lesions classed as CIN1 or CIN2, and mesenchymal, mixed epithelial/mesenchymal, melanocytic, germ cell and lymphoid/haematopoietic neoplasms were excluded. In this report, 'carcinoma of the cervix' is defined as including both invasive cervical cancer and carcinoma *in situ*/CIN3. Also, as it is likely that at least 80% of the unspecified invasive cases would be squamous cell cancers, these cases and the small number of invasive cases of other histological types were grouped with specified squamous cell carcinomas.

Women who were aged <16 or >89 years at diagnosis/pseudo-diagnosis (the date of interview or reference date for the controls) were excluded ($n = 7$). Controls who had had a hysterectomy were excluded because they are unlikely to have been at risk of developing cervical cancer, as were all women who reported no previous sexual partners, since they are unlikely to have been exposed to cervical HPV infection ($n = 27$ cases and $n = 2{,}324$ controls). Women in the Johannesburg study who were HIV positive were also excluded.

For the majority of studies data on tobacco use was recorded as smoking habits, and it was therefore assumed that all smokers would have been tobacco smokers. Current smoking was defined as smoking at the time of diagnosis or smoking that had stopped less than a year before the date of diagnosis/pseudo-diagnosis. Analyses restricted to HPV positive women were also conducted. To maximise comparability between studies, analyses of HPV data included only those women with a measurement of cervical HPV-DNA by a PCR-based method. For these studies, 'high-risk' HPV types were as defined by Muñoz *et al.*[3] where possible, or as had been defined in each study, and all these studies included tests for HPV 16 and 18. Insufficient data were available to allow analyses based on other methods of HPV detection.

Statistical methods and presentation of data

Conditional logistic regression was used to calculate relative risks (RRs) and their corresponding 95% confidence intervals (CIs). When only 2 groups are compared the RR of cervical cancer and the associated CI are presented. However, when more than 2 groups are compared variances are estimated by treating the RRs as floating absolute risks.[4] Use of floating methods does not alter the estimates of RR, but yields floated standard errors and floated CIs (FCIs) that enable valid comparisons to be made between any 2 exposure groups, even if neither is the baseline group. The unfloated (*i.e.* 'conventional') CIs are quoted, however, whenever results for all of the exposure groups are not presented for comparison (*e.g.*, when quoted in the text). Tests for trend were carried out in smokers using the median time since stopping, amount smoked, age at starting or duration of smoking in the controls within a given category as the level for that category. Heterogeneity tests were calculated using the method of weighted least squares, with weights defined as the inverse of the variance of the log RRs.

Women were stratified by study, and within study by centre and by single years of age, to ensure that comparisons were only made between women of the same age from the same study or centre. All analyses were additionally stratified by age at first intercourse (<18, 18–20 and ≥21 years), duration of oral contraceptive use (never, <10 and ≥10 years use), number of full-term pregnancies (0, 1–2, 3–4 and ≥5) and by lifetime number of sexual partners (1, 2–5 and ≥6). Finer stratification was not possible for number of sexual partners because several studies had not collected more detailed information on this variable. If studies had used alternative categorisations from these, then the midpoint of the alternative category was used to allocate the data to the categories given above. Where studies or individual women were missing information on any of these variables, they were included by creating a category for 'missing' for the relevant variable. However, as a sensitivity analysis of this assumption about missing data found that the number of sexual partners was a highly significant confounding factor, women without information on this key variable were excluded from calculations of all summary RRs.

Many studies included shared controls for cases of invasive cancer and carcinoma *in situ*/CIN3 and for invasive adenocarcinoma and squamous cell carcinoma. Therefore, where direct comparisons were made between cancer types (heterogeneity tests), a case–case analysis was used.

Presentation of results

Where results are presented in the form of plots, RRs are represented by squares and their corresponding FCI/CIs by horizontal lines. The position of the square indicates the point estimate of the RR, and the area of the square is inversely proportional to the variance of the logarithm of the RR, thus providing an indication of the amount of statistical information available for that particular estimate. Where summary RRs have been calculated, these are shown as open diamonds, whose horizontal extent indicates the 95% FCI/CI.

Results

In total, individual data from 23[5–39] published studies were analysed, which included a total of 13,541 women with carcinoma of the cervix (9,052 women with invasive cancer and 4,489 women with carcinoma *in situ*/CIN3) and 23,017 women without carcinoma of the cervix with data on smoking status (Table I). The studies came from 4 continents, with approximately half of the studies being from less developed countries. Median age at diagnosis for the invasive cancers was 46 years, whilst for the carcinoma *in situ*/CIN3 cases it was 35 years. Histology was available for all but 477 cases of invasive cancer, with 84% of specified invasive cancers being squamous cell carcinomas and 15% adenocarcinomas. In general, histological type was not provided for the cases of carcinoma *in situ*/CIN3, although there were 295 specified cases of adenocarcinoma *in situ*.

As well as information on smoking status, most of the studies had also collected information on the age at starting and stopping smoking, the duration of smoking and the average number of cigarettes smoked per day. The percentage of controls who were current smokers varied between studies from 0 to 60% (Table I). In controls who had ever smoked, the mean number of cigarettes smoked ranged in each study from 3 to 19 per day. In general, the proportion of ever smokers and the average number of cigarettes smoked per day was considerably higher in the studies conducted in more developed countries, compared with those in the less developed countries (47% compared to 13% and mean = 14 compared to 8 per day, respectively).

TABLE I – CHARACTERISTICS OF THE 23 STUDIES INCLUDED IN THIS ANALYSIS

Study name	Country	Cases		Controls	Median year of diagnosis	Median age at diagnosis	% Current smokers	Average cigarettes/day*	Sexual partners†	HPV method
		Invasive	*In situ*							
Cohort studies										
Oxford FPA[5]	UK	42	0	154	1983	40	34	na	n	none
Tromsφ23[6]	Norway	0	197	806	1983	32	56	11	n	none
Sweden[7]	Sweden	0	378	378	1987	34	36	9	y	PCR
Manchester‡[8]	UK	0	199	181	1990	32	49	14	y	PCR
Copenhagen[9]	Denmark	0	190	754	1992	26	49	14	y	PCR
Portland Kaiser[10]	USA	0	65	261	1992	31	19	14	y	PCR
Guanacaste[11]	Costa Rica	39	129	683	1993	38	5	7	y	PCR/HC
Million Women Study[12]	UK	184	516	2800	1999	56	19	14	n	none
Case–control, population controls										
Los Angeles squamous[13]	USA	200	0	198	1981	44	22	16	y	none
Brinton USA[14]	USA	479	291	790	1983	41	33	19	y	none
London CIN[15]	UK	0	224	528	1985	29	38	13	y	none
Male factor[16]	Denmark	59	584	598	1985	31	60	15	y	none
Los Angeles adeno[17]	USA	141	53	373	1986	37	28	17	y	none
UK cervical cancer[18]	UK	578	0	928	1986	35	38	12	y	serology
IARC	Colombia[19]	217	0	177	1987	45	17	11	y	PCR
	Spain[19]	248	0	231	1987	53	10	10	y	PCR
North Thames invasive[20]	UK	119	0	242	1988	34	33	15	y	none
Daling Seattle[21,22]	USA	677	189	1422	1992	40	24	16	y	Serology
USA adeno[23]	USA	184	80	300	1994	38	23	15	y	PCR
Case–control, hospital controls										
WHO[24]	Chile	17	21	202	1985	43	27	6	y	none
	Mexico	107	48	578	1985	43	20	5	y	none
	Thailand (Chulalongkorn)	295	144	1159	1986	42	9	11	y	none
	Thailand (Siriraj)	364	246	1279	1986	41	6	10	y	none
	Thailand (Chiang Mai)	490	133	1461	1986	43	10	6	y	none
Milan[25,26]	Italy (invasive)	781	0	878	1985	53	23	13	y	none
	Italy *(in situ)*	0	270	303	1985	40	32	12	y	none
Brinton Latin America[27]	Colombia	213	0	408	1986	47	23	11	y	FISH
	Costa Rica	192	0	365	1986	44	15	11	y	FISH
	Mexico	155	0	290	1986	45	22	5	y	FISH
	Panama	194	0	309	1986	48	6	6	y	FISH
IARC	Colombia[28]	0	234	269	1986	37	15	10	y	PCR
	Spain[28]	0	222	241	1987	34	34	9	y	PCR
	Paraguay[29]	115	0	100	1989	49	16	3	y	PCR
	Brazil[30]	199	0	225	1990	50	22	10	y	PCR
	Thailand[31]	386	0	354	1991	49	5	5	y	PCR
	Mali[32]	82	0	97	1992	45	9	na	y	PCR
	Philippines[33]	387	0	386	1992	47	4	8	y	PCR
	Morocco[34]	214	0	203	1993	49	2	7	y	PCR
	Peru[35]	198	0	196	1996	48	2	7	y	PCR
	Algeria[36]	198	0	202	1998	53	2	10	y	PCR
	Chennai[37]	205	0	213	1998	47	0	na	y	PCR
Bangkok[38]	Thailand[38]	288	76	761	1992	42	3	7	y	PCR
Johannesburg[39]	South Africa	805	0	734	1997	52	6	8	y	serology
Total		9052	4489	23017	1987	42	15	13	—	—

PCR, polymerase chain reaction; HC, Hybrid capture; FISH, filter *in situ* hybridisation; y, yes; n, no; na, not available. Smoking statistics for controls only.
*For the smokers only.–†Data collected on number of sexual partners.–‡HPV positive women only.

TABLE II – ASSOCIATIONS WITH SMOKING BEHAVIOUR AMONG THE CONTROLS: RELATIVE RISK (RR)[1] AND 95% FCI/CI OF BEING A CURRENT OR PAST COMPARED TO NEVER SMOKER ACCORDING TO VARIOUS SUBGROUPS

Subgroup	Past/never smokers		Current/never smokers	
	n	RR (95% FCI/CI)	*n*	RR (95% FCI/CI)
Number of sexual partners				
1	731/8965	1.00 (0.91–1.11)	1188/8965	1.00 (0.90–1.11)
2–5	768/3621	2.09 (1.96–2.23)	1203/3621	1.84 (1.70–2.00)
≥6	576/993	4.73 (4.19–5.34)	1168/993	3.61 (3.15–4.14)
Age at first intercourse				
<18	838/3762	1.00 (0.91–1.10)	1757/3762	1.00 (0.93–1.08)
18–20	695/4313	0.66 (0.61–0.72)	1135/4313	0.53 (0.49–0.57)
≥21	468/4888	0.48 (0.43–0.54)	660/4888	0.35 (0.32–0.38)
HPV				
−ve	799/5071	1.00	1268/5071	1.00
+ve high risk	192/807	1.22 (0.99–1.50)[2]	241/807	1.04 (0.86–1.26)[2]
Number of Pap smears				
0	276/4966	1.00	645/4966	1.00
≥1	1328/6425	0.96 (0.83–1.10)[2]	2222/6425	1.39 (1.14–1.70)[2]
Number of full-term pregnancies				
0	480/2140	1.00 (0.88–1.14)	1110/2140	1.00 (0.89–1.12)
1–4	2081/10372	1.13 (1.08–1.18)	2862/10372	1.08 (1.04–1.12)
≥5	353/3226	1.06 (0.90–1.24)	451/3226	1.12 (0.97–1.29)
Age at first birth				
<19	357/2370	1.00 (0.89–1.12)	653/2370	1.00 (0.87–1.15)
19–22	817/4535	0.74 (0.69–0.80)	1279/4535	0.88 (0.81–0.96)
≥23	1227/6164	0.46 (0.42–0.49)	1339/6164	0.75 (0.69–0.81)
Years full-time education				
<10	635/7849	1.00 (0.83–1.20)	1174/7849	1.00 (0.87–1.14)
10–14	1680/5088	1.06 (1.00–1.12)	2592/5088	0.92 (0.87–0.97)
≥15	537/1670	0.85 (0.75–0.95)	414/1670	0.42 (0.37–0.48)
Condom use				
Never	1105/9227	1.00	1954/9227	1.00
Ever	796/3083	1.02 (0.89–1.16)[2]	1528/3083	0.82 (0.74–0.92)[2]
Duration of OC use				
Never	1079/8225	1.00 (0.91–1.10)	1485/8225	1.00 (0.92–1.08)
<10 years	1469/6274	1.39 (1.29–1.48)	2378/6274	1.33 (1.25–1.41)
≥10 years	325/985	1.55 (1.38–1.78)	484/985	1.80 (1.58–2.04)

[1]RR stratified by study and age.–[2]Where only 2 strata are available (*e.g.* never/ever) 95% CIs are presented rather than FCIs.

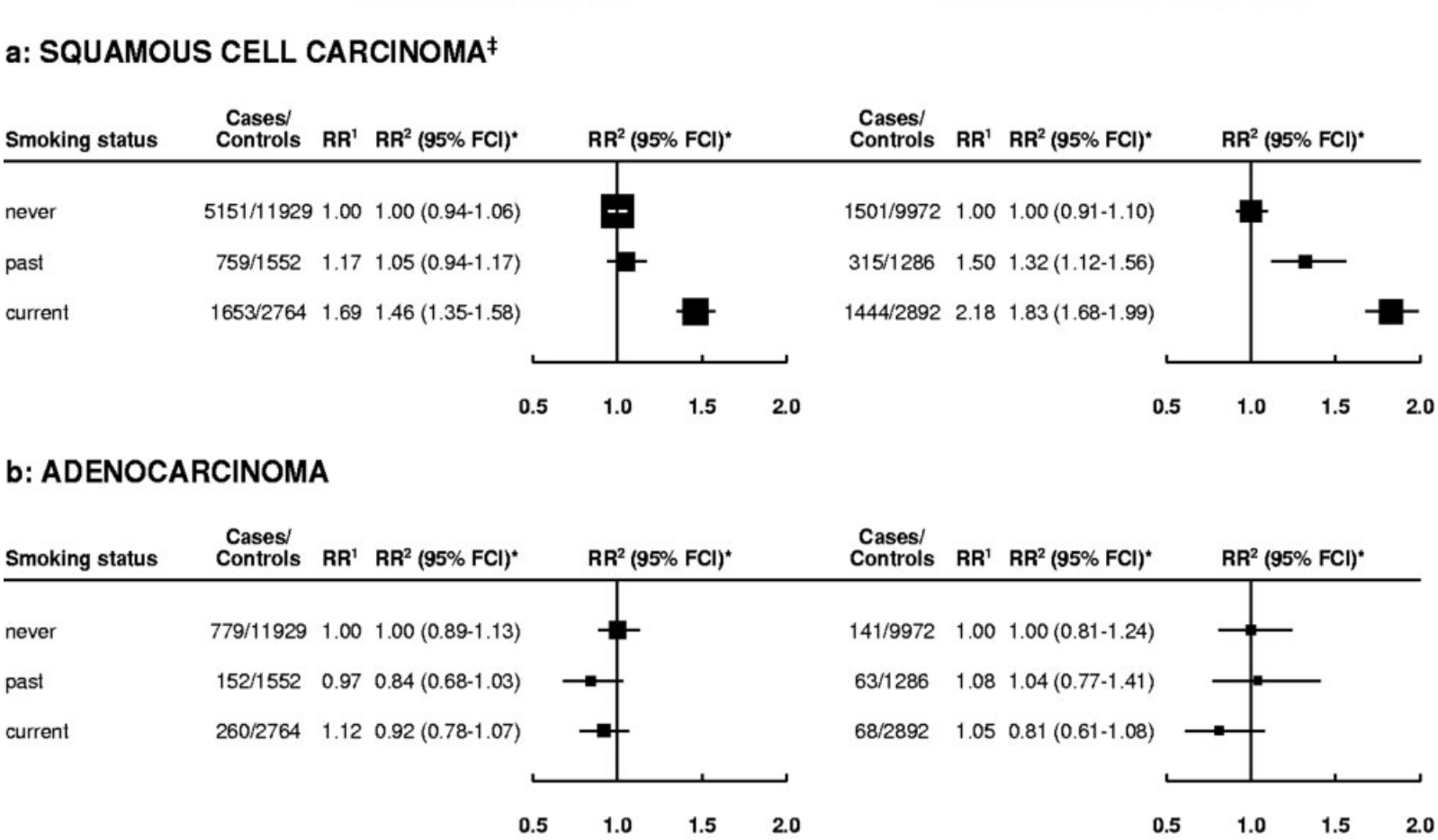
In the controls, the likelihood of being a current or past smoker was strongly related to the number of sexual partners and to the age at first intercourse (Table II). However, there was no evidence that current smokers were more likely to test positive for a high-risk type HPV than never smokers. Controls who had used oral contraceptives were also more likely to be current or past smokers, whereas those who had a later age at first birth or more full-time education were less likely to be current or past smokers.

Current smokers had a significantly increased risk of squamous cell carcinoma compared to never smokers (summary RR for invasive cancer = 1.46 (95% CI: 1.32–1.61) and for carcinoma *in situ*/CIN3 = 1.83 (1.61–2.08), (Fig. 1*a*). The risks for past smokers were lower (RR for invasive cancer = 1.05 (0.92–1.19) and for carcinoma *in situ*/CIN3 = 1.32 (1.09–1.60), although there was no trend with time since stopping smoking (p-trend = 0.6 and 0.5, respectively) (Appendix A). (The CIs quoted in the text are 'conventional' CIs and are therefore somewhat wider than the floating CIs given in the figures (see Material and Methods)). Neither current nor past smokers were at increased risk of adenocarcinoma of the cervix (current smoking RR for invasive adenocarcinoma = 0.92 (0.75–1.12) and adenocarcinoma *in situ* = 0.81 (0.57–1.16), (Fig. 1*b*).

Although the RRs of squamous cell carcinoma *in situ*/CIN3 for current and past smoking appeared to be somewhat higher than the risks for invasive squamous cell cervical cancer, when these cases were compared directly (in the studies in which such a comparison was possible), the differences were not statistically significant (p = 0.7 and 0.7, respectively). Neither were there differences on case–case analysis between the risks for invasive and *in situ* adenocarcinomas for current or past smoking (p = 0.3 and 0.4, respectively). Hence, cases of invasive cancer and of carcinoma *in situ*/CIN3 were combined in all subsequent analyses and are referred to as carcinomas. The RRs for current and past smoking for all squamous cell carcinomas combined were 1.60 (1.48–1.73) and 1.12 (1.01–1.25) respectively (p-trend for time since stopping in past smokers = 0.6); for all adenocarcinomas combined, the respective RRs were 0.89 (0.74–1.06) and 0.89 (0.72–1.10). In a case–case analysis, the differences between these risks for squamous cell and for adenocarcinoma were statistically significant (for current smoking $p<0.001$ and for past smoking p = 0.01). In all subsequent analyses therefore, risks are presented separately for squamous cell carcinoma and adenocarcinoma of the cervix.

To illustrate the effect of the 4 potential confounding factors for which adjustment was made (lifetime number of sexual partners, age at first intercourse, parity and oral contraceptive use), RRs stratified only by age and study are also given in the figures. The effect of including different stratification variables on the smoking risks was investigated in the subset of women for whom data on all potential stratification variables were available. Stratification by sexual partners was the only factor that materially altered the risks (Table IIIa). When current smokers were compared to never smokers, the RR for squamous cell carcinoma of the cervix was 1.78 (95% CI: 1.65–1.93) before stratification by the number of sexual partners, and declined to 1.50 (1.38–1.63) after stratification. The corresponding χ^2_2 value for smoking status declined by 60% from 222.4 to 92.4, indicating that number of sexual partners is a major confounding factor in the relationship between smoking and carcinoma of the cervix. The RRs for adenocarcinoma were affected similarly, being reduced after stratification by number of sexual partners, but not altered materially after further stratification by any other available factor (Table IIIb).

In current smokers, the RR of squamous cell carcinoma increased with increasing number of cigarettes smoked per day (≥15 per day *versus* never smoker RR = 1.98 (1.78–2.21),



* RR^1 stratified by study and age at diagnosis only. RR^2 stratified by study, age at diagnosis, number of sexual partners, duration of oral contraceptive use, age at first intercourse and number of births; 95% floated confidence intervals (FCIs) for RR^2. Women with no information on number of sexual partners are excluded from these analyses.

‡ includes all non-adenocarcinomas

Figure 1 – Relative risk (RR)* of carcinoma of the cervix by histological type in relation to smoking status.

TABLE III – EFFECT OF ADDITIONAL STRATIFICATION BY POTENTIAL CONFOUNDING FACTORS ON THE RR (95% CI) OF CARCINOMA OF THE CERVIX[1] IN RELATION TO SMOKING STATUS

Stratification variables	RR (95% CI)		χ^2_2
	Past *vs.* never smoking	Current *vs.* never smoking	
a) Squamous cell carcinoma[2]			
Age + study	1.25 (1.13–1.39)	1.78 (1.65–1.93)	222.4
Age + study + sexual partners	1.11 (1.00–1.24)	1.50 (1.38–1.63)	92.4
Age + study + sexual partners + age at first intercourse	1.03 (0.91–1.16)	1.43 (1.31–1.56)	66.8
Age + study + sexual partners + age at first birth	1.02 (0.90–1.16)	1.34 (1.22–1.47)	40.0
Age + study + sexual partners + parity	1.15 (1.02–1.29)	1.50 (1.37–1.64)	78.4
Age + study + sexual partners + OC use	1.11 (0.99–1.24)	1.51 (1.39–1.65)	89.1
Age + study + sexual partners + pap smears	1.14 (1.02–1.28)	1.54 (1.41–1.68)	96.9
b) Adenocarcinoma			
Age + study	0.96 (0.80–1.16)	1.09 (0.93–1.28)	1.8
Age + study + sexual partners	0.84 (0.69–1.04)	0.91 (0.77–1.08)	3.0
Age + study + sexual partners + age at first intercourse	0.78 (0.63–0.97)	0.87 (0.73–1.04)	5.8
Age + study + sexual partners + age at first birth	0.82 (0.65–1.02)	0.86 (0.71–1.04)	4.3
Age + study + sexual partners + parity	0.84 (0.68–1.05)	0.90 (0.75–1.07)	2.9
Age + study + sexual partners + OC use	0.78 (0.63–0.97)	0.90 (0.76–1.08)	5.3
Age + study + sexual partners + pap smears	0.88 (0.71–1.08)	0.92 (0.77–1.09)	1.9

Only women with available data on all variables were included in these analyses.
[1]Includes invasive and carcinoma *in situ*/CIN3.–[2]Includes all non-adenocarcinomas.

p-trend<0.001), whereas there was no evidence of such a trend for past smokers (*p*-trend = 0.1) (Fig. 2). The risk of adenocarcinoma was not related to amount smoked in current or past smokers (*p*-trend = 0.3 and 0.07, respectively). There was also evidence of an increasing risk of squamous cell carcinoma with decreasing age at starting smoking for current smokers, but not for past smokers (RR for age at starting <16 years compared to ≥20 years = 2.00 (1.77–2.27), *p*-trend<0.001 and 1.17 (0.95–1.43), *p*-trend = 0.7, respectively) (Appendix B). However, there was no evidence of an association between risk of squamous cell carcinoma and duration of smoking (*p*-trend = 0.3 (current smokers) and 0.4 (past smokers), Fig. 3). The risk of adenocarcinoma was not associated with age at starting or duration of smoking (*p*-trend=0.9 and 0.3 (age at starting) and 0.3 and 0.2 (duration) in current and past smokers, respectively).

There were 8 studies with a PCR-based measure of cervical HPV-DNA (Table I). On average, in these studies, 68% of cases tested positive for high-risk HPV-DNA (study range=38–99%) and the studies with lowest proportions of cases testing positive were the earlier studies, conducted when the tests were less sensitive. In analyses restricted to the women from these studies who tested positive for a high-risk HPV type, the pattern of risk of squamous cell carcinoma with respect to smoking status was similar to that seen for all women in these studies (Fig. 4*a*). There was a significantly increased risk of squamous cell carcinoma in current smokers (RR = 1.95(1.43–2.65)) and a lower risk in past smokers (RR = 1.64 (0.99–2.72)). The CIs in this analysis are relatively wide due to the small number of controls who had ever smoked and who tested positive for HPV-DNA (n = 290). Thus, even in this large dataset, it was not possible to perform detailed analyses of smoking behaviour in HPV positive women. This was also a problem for the analysis of adenocarcinoma risk, as there were only 31 adenocarcinoma cases who had ever smoked and who tested positive for HPV-DNA (RR for current *versus* past smoking = 1.06 (95% CI: 0.14–7.96)) (Fig. 4*b*).

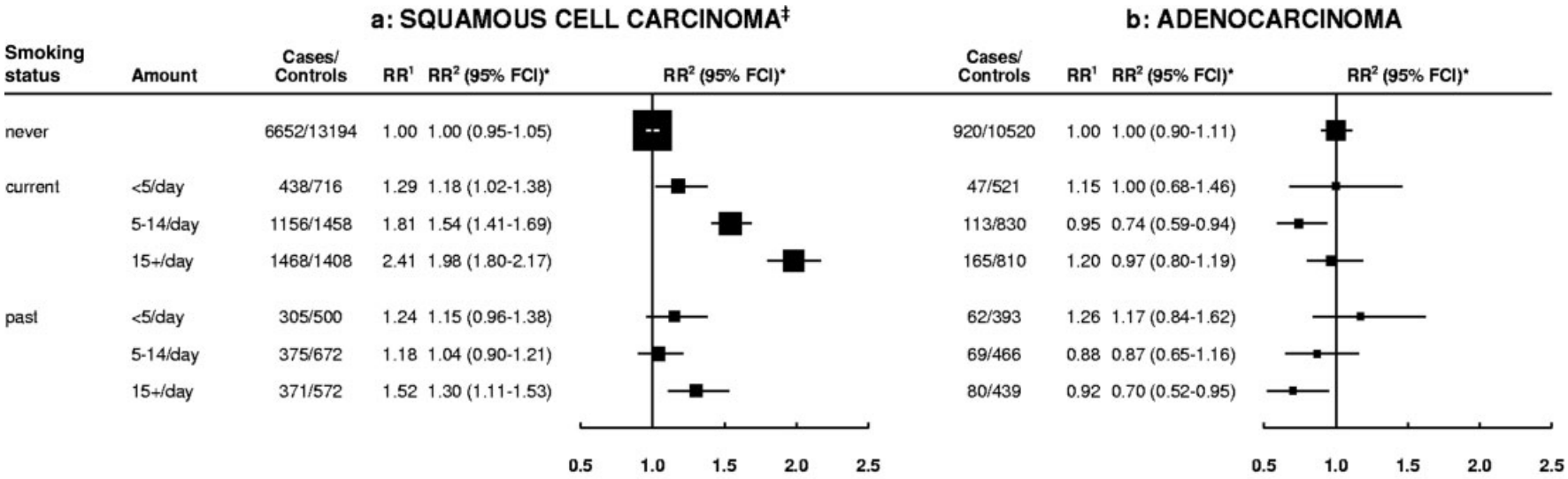
Figure 5 shows the study-specific results for the risk of squamous cell carcinoma for current and past smoking compared to never smoking. There was significant heterogeneity between the studies with respect to the risk associated with current smoking (χ^2_{18} = 75.1, p <0.001), at least half of which was accounted for by heterogeneity according to study design (χ^2_2 = 40.9, $p < 0.001$) and this heterogeneity was not reduced by additional adjustment for amount smoked (data not shown). The population-based case–control studies had the highest summary RR and the hospital-based case–control studies the lowest (current *versus* never smoking RRs = 2.03 (1.79–2.29) and 1.20 (1.06–1.36), respectively). There was no significant heterogeneity between the individual study results for adenocarcinoma with respect to past or current smoking (p = 0.6 and 0.3, respectively) (Appendix C)

Discussion

This pooled analysis of individual data from 23 epidemiological studies is the largest and most detailed investigation to date of the risk of carcinoma of the cervix in relation to tobacco smoking. The results provide evidence that current smokers, compared to never smokers, are at a significantly increased risk of developing squamous cell cervical carcinoma and that this risk increases with the number of cigarettes smoked per day and with decreasing age at starting smoking. Past smokers had a lower risk of squamous cell carcinoma than current smokers, but there was no trend in risk with time since stopping smoking. The pattern of risk for smoking was similar for invasive cervical cancer and for carcinoma *in situ*/CIN3. Squamous cell carcinomas account for about 80% of cases of cervical cancer in most populations; most of the remaining cases are adenocarcinomas. Smoking was not found to increase the risk of adenocarcinoma of the cervix.

The studies that were combined in this pooled analysis included about 70% of the published worldwide data on smoking and cervical cancer. Seven case–control studies were eligible but were not included because the data were not available.[40–46] RRs and CIs were published for 4 of these studies and the summary RR for current smoking was 1.73 (95% CI: 1.21–2.46). Since the results from the studies that were not included were broadly similar to the findings from those studies that were included, their omission is unlikely to have biased the results presented here.

There was significant heterogeneity between the results from different studies and between study designs, with the highest RRs for current smoking in the population-based case–control studies and the lowest in the hospital-based case–control studies. A possible reason for this is that smokers were overrepresented in the controls in the hospital-based case–control studies due to inclusion of women with smoking-related conditions, and underrepresented in the population-based case–control studies due to the reluctance of smokers to participate in such studies. Also, as 78% of the women who reported only 1 sexual partner were in hospital-based case–control studies, it is possible that the differences according to study design were related to confounding by sexual partners. However, in subgroup analyses according to number of sexual partners (1, 2–5, ≥6), the differences according to study design



* RR1 stratified by study and age at diagnosis only. RR2 stratified by study, age at diagnosis, number of sexual partners, duration of oral contraceptive use, age at first intercourse and number of full-term pregnancies; 95% floated confidence intervals (FCIs) for RR2. Women with no information on number of sexual partners are excluded from these analyses.

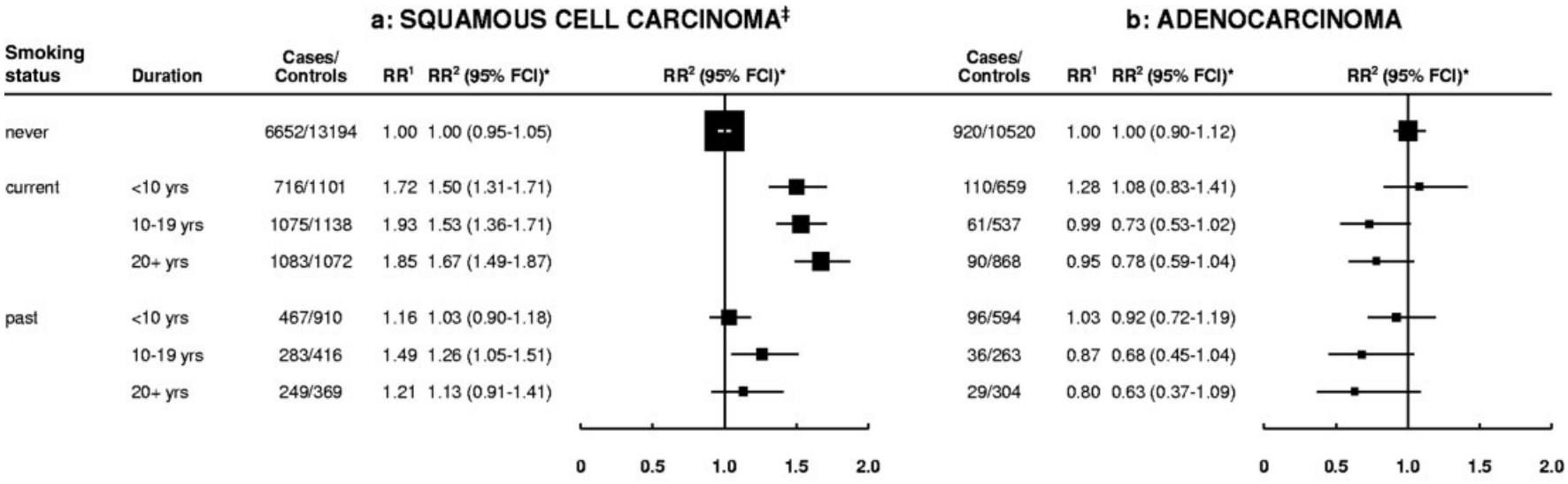
a: p-trend for current smokers<0.001; for past smokers=0.1

b: p-trend for current smokers=0.3; for past smokers=0.07

† invasive and carcinoma in situ/CIN3

‡ includes all non-adenocarcinomas

FIGURE 2 – Relative risk (RR)* of carcinoma of the cervix† in relation to smoking status and amount smoked.



* RR^1 stratified by study and age at diagnosis only. RR^2 stratified by study, age at diagnosis, number of sexual partners, duration of oral contraceptive use, age at first intercourse and number of full-term pregnancies; 95% floated confidence intervals (FCIs) for RR^2. Women with no information on number of sexual partners are excluded from these analyses.

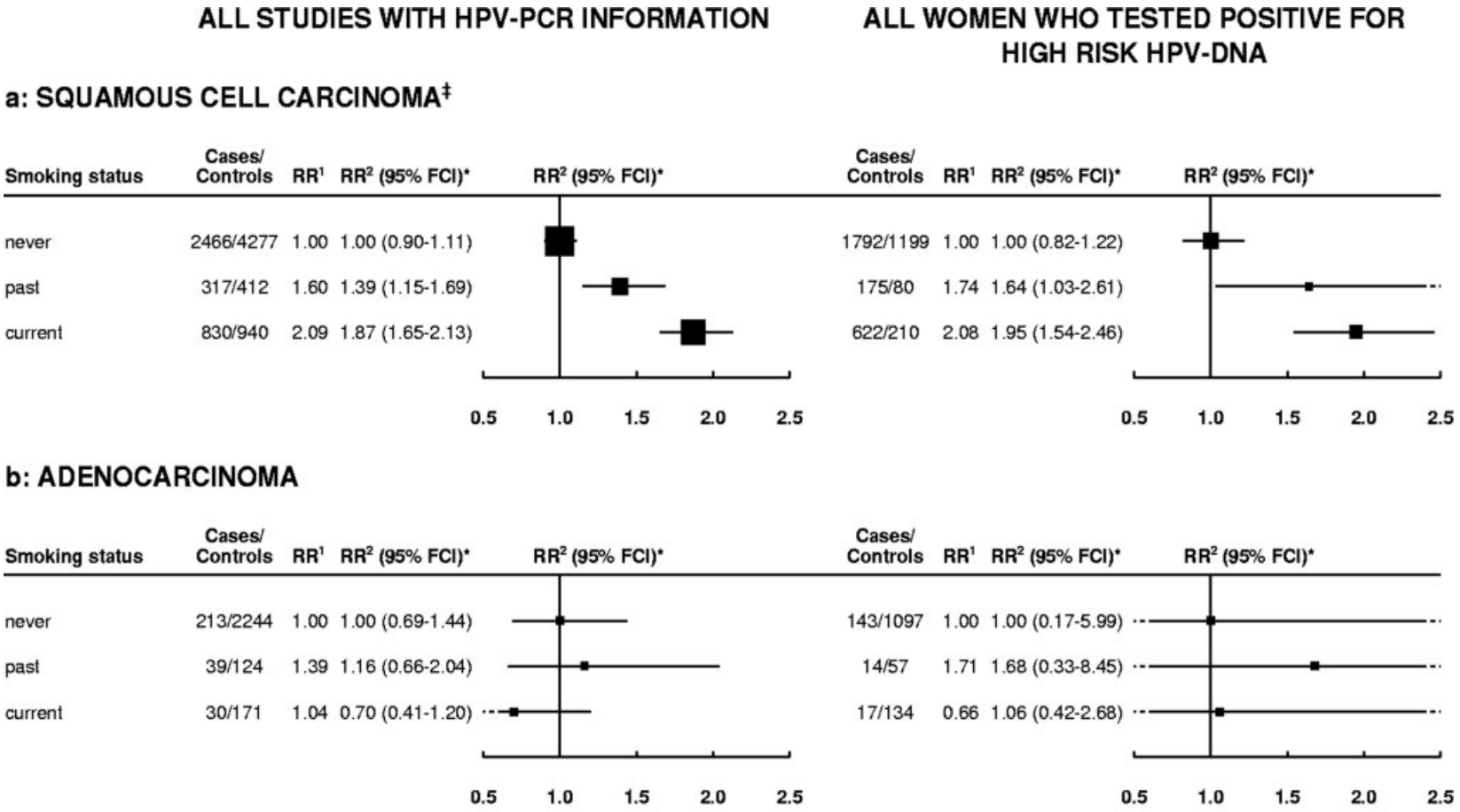
a: p-trend for current smokers=0.3; for past smokers=0.4

b: p-trend for current smokers=0.3; for past smokers=0.2

† invasive and carcinoma in situ/CIN3

‡ includes all non-adenocarcinomas

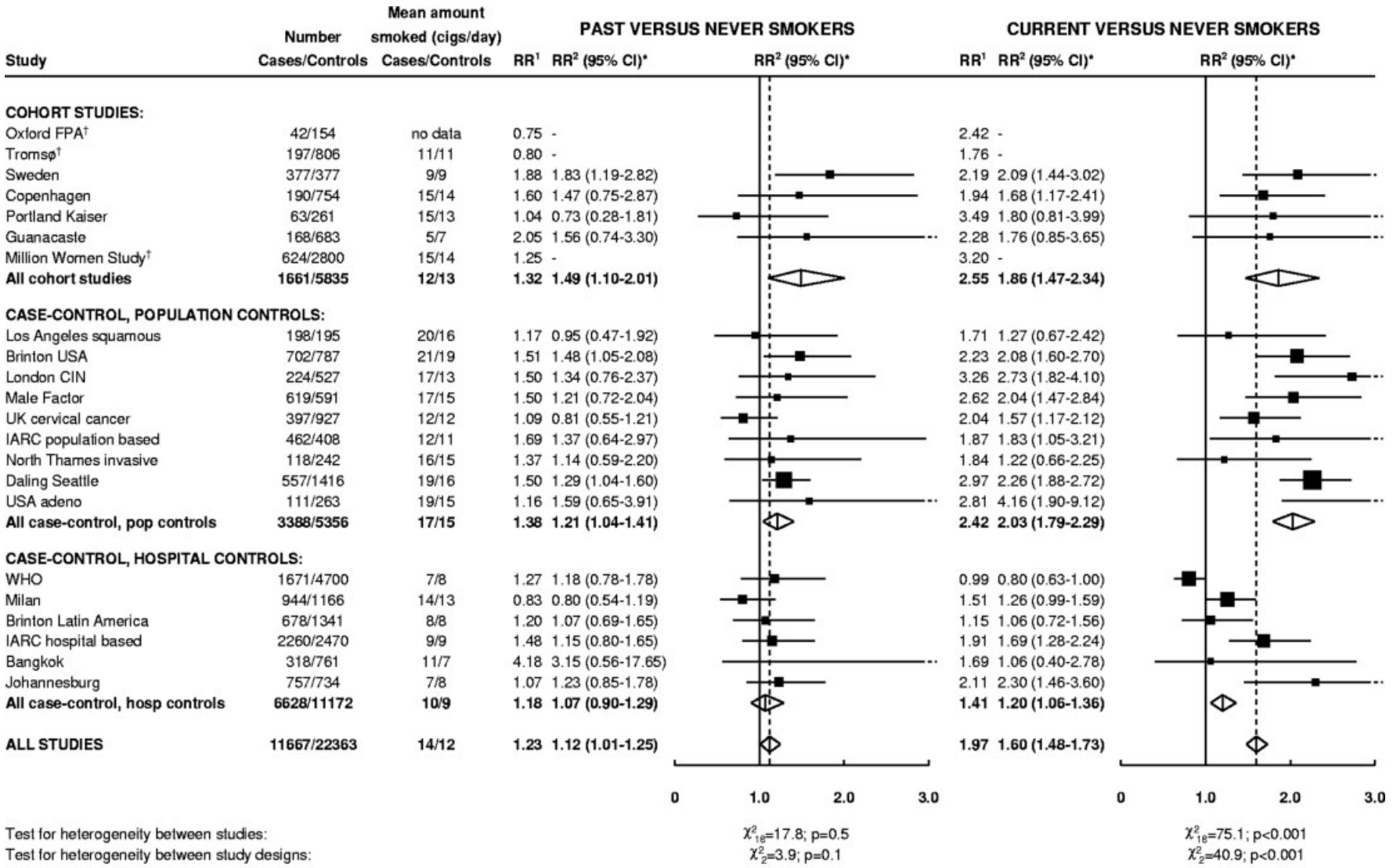
Figure 3 – Relative risk (RR)* of carcinoma of the cervix† in relation to smoking status and duration of smoking.



* RR[1] stratified by study and age at diagnosis only. RR[2] stratified by study, age at diagnosis, number of sexual partners, duration of oral contraceptive use, age at first intercourse and number of births; 95% floated confidence intervals (FCIs) for RR[2]. Women with no information on number of sexual partners are excluded from these analyses.

‡ invasive and carcinoma in situ/CIN3 (includes all non-adenocarcinomas)

FIGURE 4 – Relative risk (RR)* of carcinoma of the cervix in relation to smoking status and high-risk HPV positivity.



* RR1 stratified by study and age at diagnosis only (includes studies with no data on number of sexual partners and so risks may differ from those in Figure 1). RR2 stratified by study, age at diagnosis, number of sexual partners, duration of oral contraceptive use, age at first intercourse and number of full-term pregnancies. CI - confidence interval.

† no adjustment for number of sexual partners (data not available)

‡ invasive and carcinoma in situ/CIN3 (includes all non-adenocarcinomas)

FIGURE 5 – Relative risk (RR)* of squamous cell carcinoma of the cervix‡ in relation to smoking status by study.

were still present. For example, for the subgroup of women who reported 1 sexual partner, the RRs for current *versus* never smoking were 1.75 (95% CI: 0.73–4.19) for cohort studies, 2.27 (1.71–3.01) for population-based case–control studies and 1.11 (0.95–1.30) for hospital-based case–control studies. Therefore confounding by number of sexual partners does not seem to be the main reason for the differences in the results according to study design.

In several recent studies of smoking and cervical cancer, the emphasis has been on the potential confounding between smoking and cervical HPV infection, the main cause of cervical cancer. The approach used in those studies was to restrict analysis to women who tested positive for cervical HPV-DNA. In the current study there was evidence of a significantly increased risk of squamous cell cervical carcinoma for current smokers in analyses restricted to women who tested positive for a high-risk HPV type. However, most studies only test for HPV-DNA at one point in time, and because controls who test positive at one point in time are more likely to have a transient infection, whereas cases are likely to have a persistent infection, this could be a biased measure of HPV infection. Restriction to women who test positive for HPV also restricts the posed scientific question to be whether or not smoking increases the risk of disease progression in women who are already infected with HPV. However, smoking could act to increase the risk of cervical cancer at other stages of the natural history of the disease, for example by increasing the probability of becoming infected given exposure to HPV, or of developing a persistent cervical HPV infection. In this paper, the main aim was to investigate the broader question of whether smoking increases the risk of cervical cancer in women who are equally likely to have been exposed to, rather than infected with, HPV. This was investigated by stratification by number of sexual partners, the main determinant of exposure to HPV. This stratification substantially reduced the magnitude of the association between smoking and squamous cell carcinoma, and as the reported number of number of sexual partners is not an ideal measure of exposure to HPV and was categorised relatively crudely (1, 2–5 and $\geq$6), there is likely to be some residual confounding with respect to exposure to HPV.

In current smokers, the risk increased with younger age at starting smoking, but was not associated with duration of smoking. This may seem surprising, as duration of smoking is often defined as current age or age at stopping smoking minus age at starting smoking. However, in many of these studies, duration of smoking was reported by the woman rather than calculated as described above. Although this allows for periods of cessation to be taken into account, it also tended to result in rounding of reported duration (*e.g.*, 5 years, 10 years, *etc.*). It is possible, therefore, that duration of smoking was reported less accurately than age at starting smoking and that this variability obscured an association; alternatively it is possible that smoking duration does not independently influence the risk of developing the disease. It was not feasible to differentiate between these 2 possibilities on the basis of the current epidemiological evidence. Also, although the risk in past smokers was lower than that in current smokers and overall there were no clear trends with respect to amount smoked or age at starting smoking in the past smokers, there was some heterogeneity in results according to study design. Therefore the risk associated with past smoking and how quickly the risk might decline after stopping smoking remain uncertain.

Some other epithelial cancers, for example those of the nasal cavity, the oesophagus and possibly the lung, also appear to show differences between squamous cell and adenocarcinoma in relation to smoking, with the effect of smoking being greater for squamous cell tumours.[1] However, the lack of an association between adenocarcinoma of the cervix and current smoking does raise the question of whether there is a particular bias that affects the 2 histological types differently. As the main cause of all cervical cancers is the sexually transmitted HPV,[47] it is unlikely that differences in confounding by number of sexual partners are responsible for the observed differences between the risks of squamous cell and adenocarcinoma of the cervix with respect to smoking. Another potential confounding factor is a previous history of cervical screening, since most cervical screening techniques are less effective at detecting adenocarcinomas than squamous cell carcinomas.[48] For the observed difference between the RR of current smoking and these 2 histological types to be due to differential screening, current smoking would have to be associated with decreased attendance at cervical screening. Although detailed screening histories were not available for these studies, there was no evidence in the controls that women who had had previous Pap smears were more or less likely to be current smokers than women who had not had previous Pap smears (Table I), and additional stratification by this variable had very little effect on the RR of squamous cell carcinoma or adenocarcinoma for current *versus* never smokers. Hence, the observed difference between the effects of current smoking on the risk of squamous cell and adenocarcinoma of the cervix does not seem to be due to confounding by screening.

In conclusion, this pooled analysis of data from about 14,000 women with carcinoma of the cervix suggests that women who are smokers have an increased risk of developing squamous cell but not adenocarcinoma of the cervix. The risk of squamous cell carcinoma increased in current smokers with the number of cigarettes smoked per day and with younger age at starting smoking. However, because of the significant heterogeneity between studies and the likelihood of residual confounding with respect to exposure to HPV infection, the magnitude of this risk remains uncertain and the contribution that tobacco smoking makes to the worldwide burden of cervical cancer cannot be accurately quantified.

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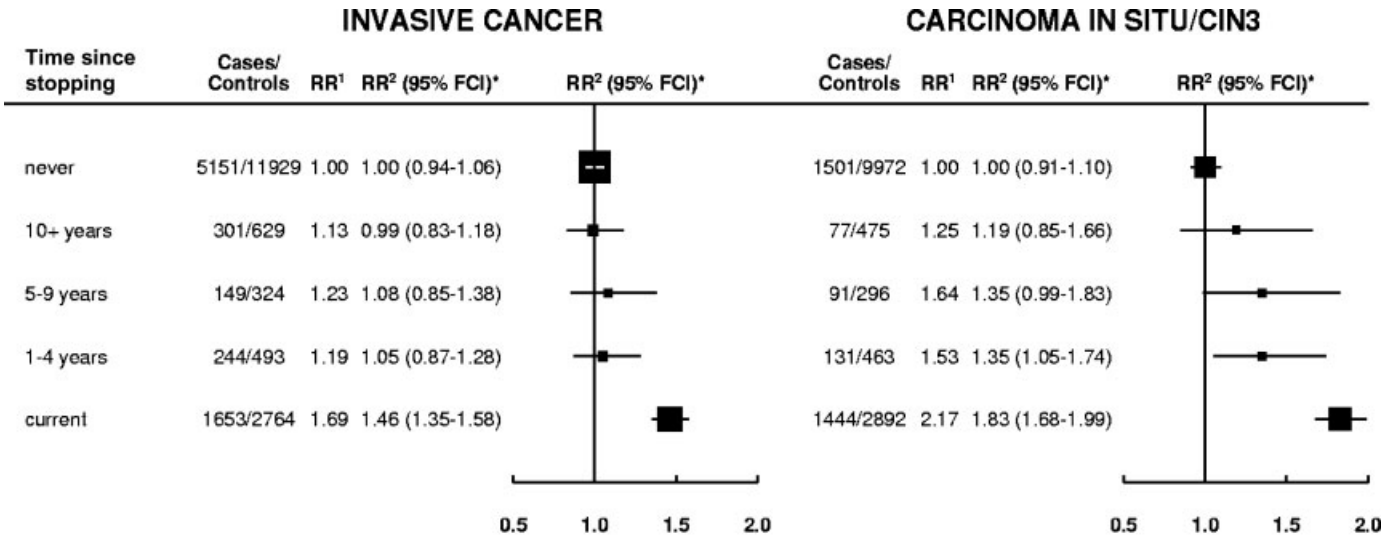
Appendix A–Relative Risk (RR)* of squamous cell carcinoma of the cervix‡ in relation to time since stopping smoking

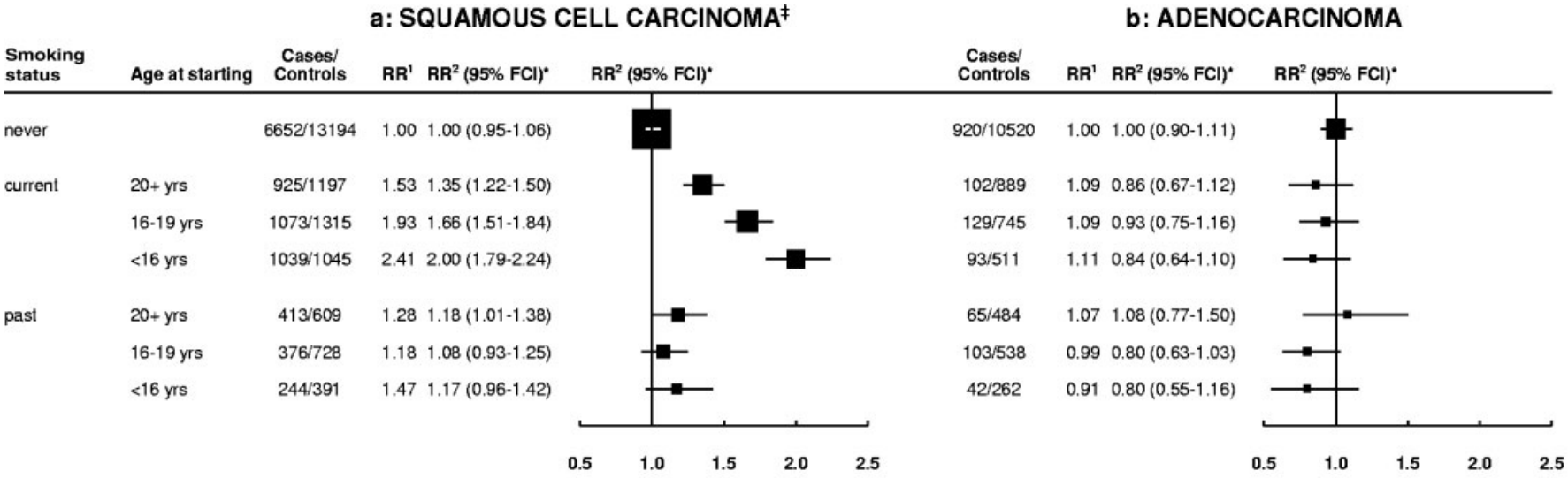


* RR^1 stratified by study and age at diagnosis only. RR^2 stratified by study, age at diagnosis, number of sexual partners, duration of oral contraceptive use, age at first intercourse and number of full-term pregnancies; 95% floated confidence intervals (FCIs) for RR^2. Women with no information on number of sexual partners are excluded from these analyses.

Trend in past smokers=0.6 (invasive cancer) and 0.5 (carcinoma in situ/CIN3).

‡ includes all non-adenocarcinomas

Appendix B–Relative Risk (RR)* of carcinoma of the cervix† in relation to smoking status and age at starting smoking



* RR^1 stratified by study and age at diagnosis only. RR^2 stratified by study, age at diagnosis, number of sexual partners, duration of oral contraceptive use, age at first intercourse, number of full-term pregnancies and amount smoked (<5, 5-14 and 15+ per day); 95% floated confidence intervals (FCIs) for RR^2. Women with no information on number of sexual partners are excluded from these analyses.

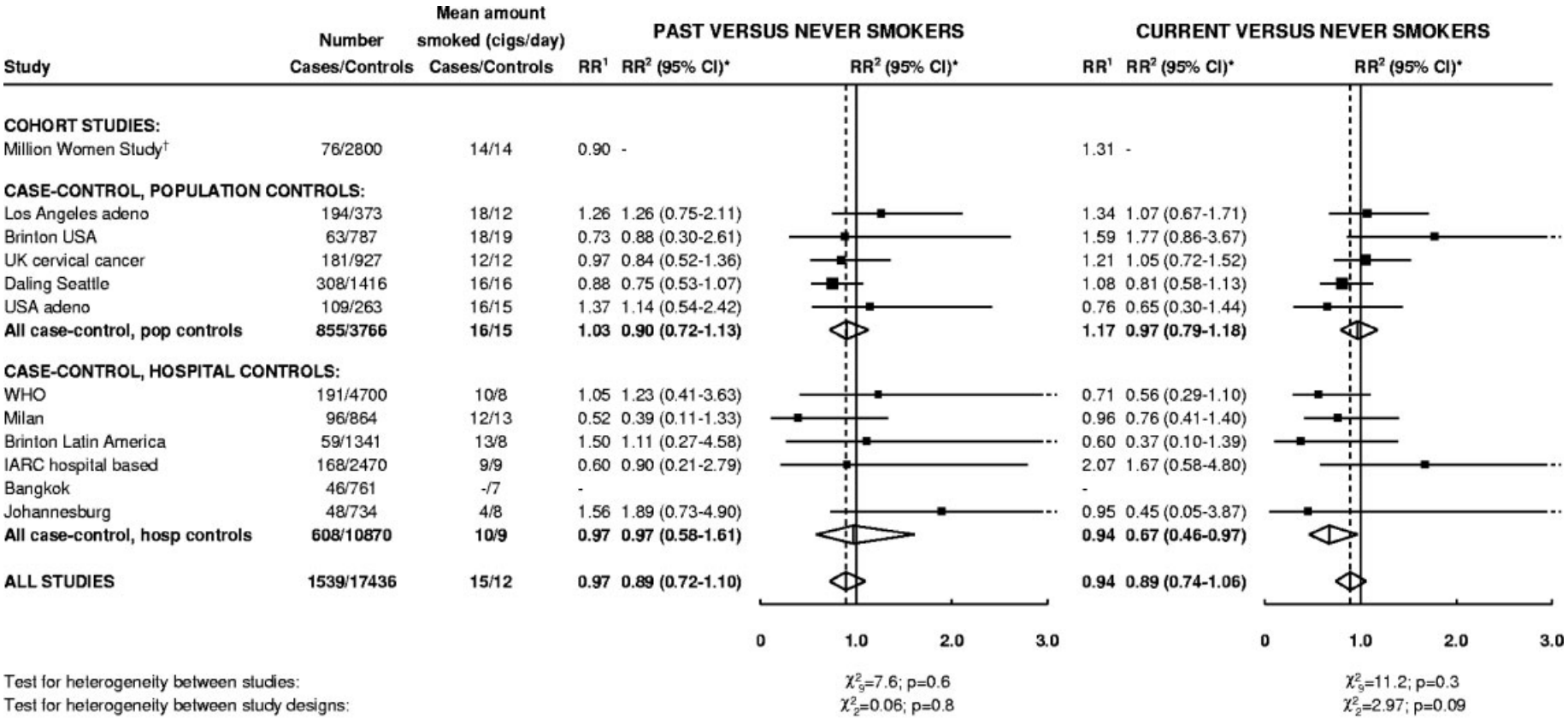
a: p-trend for current smokers<0.001; for past smokers=0.7

b: p-trend for current smokers=0.9; for past smokers=0.3

† invasive and carcinoma in situ/CIN3

‡ includes all non-adenocarcinomas

Appendix C–Relative Risk (RR)* of adenocarcinoma of the cervix† in relation to smoking status by study



Study	Number Cases/Controls	Mean amount smoked (cigs/day) Cases/Controls	PAST VERSUS NEVER SMOKERS RR[1]	PAST VERSUS NEVER SMOKERS RR[2] (95% CI)*	CURRENT VERSUS NEVER SMOKERS RR[1]	CURRENT VERSUS NEVER SMOKERS RR[2] (95% CI)*
COHORT STUDIES:						
Million Women Study†	76/2800	14/14	0.90	-	1.31	-
CASE-CONTROL, POPULATION CONTROLS:						
Los Angeles adeno	194/373	18/12	1.26	1.26 (0.75-2.11)	1.34	1.07 (0.67-1.71)
Brinton USA	63/787	18/19	0.73	0.88 (0.30-2.61)	1.59	1.77 (0.86-3.67)
UK cervical cancer	181/927	12/12	0.97	0.84 (0.52-1.36)	1.21	1.05 (0.72-1.52)
Daling Seattle	308/1416	16/16	0.88	0.75 (0.53-1.07)	1.08	0.81 (0.58-1.13)
USA adeno	109/263	16/15	1.37	1.14 (0.54-2.42)	0.76	0.65 (0.30-1.44)
All case-control, pop controls	**855/3766**	**16/15**	**1.03**	**0.90 (0.72-1.13)**	**1.17**	**0.97 (0.79-1.18)**
CASE-CONTROL, HOSPITAL CONTROLS:						
WHO	191/4700	10/8	1.05	1.23 (0.41-3.63)	0.71	0.56 (0.29-1.10)
Milan	96/864	12/13	0.52	0.39 (0.11-1.33)	0.96	0.76 (0.41-1.40)
Brinton Latin America	59/1341	13/8	1.50	1.11 (0.27-4.58)	0.60	0.37 (0.10-1.39)
IARC hospital based	168/2470	9/9	0.60	0.90 (0.21-2.79)	2.07	1.67 (0.58-4.80)
Bangkok	46/761	-/7	-		-	
Johannesburg	48/734	4/8	1.56	1.89 (0.73-4.90)	0.95	0.45 (0.05-3.87)
All case-control, hosp controls	**608/10870**	**10/9**	**0.97**	**0.97 (0.58-1.61)**	**0.94**	**0.67 (0.46-0.97)**
ALL STUDIES	**1539/17436**	**15/12**	**0.97**	**0.89 (0.72-1.10)**	**0.94**	**0.89 (0.74-1.06)**

Test for heterogeneity between studies: χ^2_9=7.6; p=0.6 | χ^2_9=11.2; p=0.3

Test for heterogeneity between study designs: χ^2_2=0.06; p=0.8 | χ^2_2=2.97; p=0.09

* RR[1] stratified by study and age at diagnosis only (includes studies with no data on number of sexual partners and so risks may differ from those in Figure 1). RR[2] stratified by study, age at diagnosis, number of sexual partners, duration of oral contraceptive use, age at first intercourse and number of full-term pregnancies. CI - confidence interval.

† no adjustment for number of sexual partners (data not available)

‡ invasive and carcinoma in situ